



Attorney Docket No. P66141US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: SCHLINGENSIEPEN et al.

Application No. 09/701,583

Group Art Unit: 1635

Filed: February 5, 2001

Examiner: J. ZARA

For: A METHOD FOR STIMULATING THE IMMUNE SYSTEM

**RESPONSE  
TO RESTRICTION REQUIREMENT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria VA 22313-1450

Sir:

This paper responds to the Office Action (restriction requirement) mailed February 5, 2004.

Pursuant to the restriction requirement under 35 USC 121, election is made, hereby, to prosecute invention Group I, claims 1-5, 7, 8, 11-13, with traverse.

TGF- $\beta$  is elected, with traverse, as the single substance from claim 1.

A tumor cell extract (specification page 5, species "m") is elected, with traverse, as the single stimulator from claim 8.

The oligonucleotide sequence TGF- $\beta$ -123-2262 (No. 7) is elected, with traverse, as the oligonucleotide sequence from claim 10.

Applicant disagrees with the finding that inventions I to IV lack unity of invention. The invention, according to claim 1, is a medicament comprising a combination of at least one inhibitor of the effect of a substance negatively effecting an immune response and at least one stimulator positively effecting an immune response. The substances negatively effecting an immune response

are selected from the Markush group comprising the targets TGF-beta, VEGF, interleukin 10, PGE2 and their respective receptors. A Markush group is a common tool to describe a related group in patents. The common effect of inhibiting one or more of these substances is to antagonize their negative effect on the immune system. In other words, the suppression of the immune system caused by each of these substances is lifted.

This common inhibiting effect can be reached by inhibiting the activating cascade of those substances in different ways, which is referred to in claims 2-6. One way is the inhibition of the synthesis of targets such as TGF-beta, VEGF, interleukin 10, PGE2 and their respective receptors by antisense oligonucleotides (claim 4). Antisense oligonucleotides hybridize with the m-RNA of their specific target and, thus, inhibit the formation of those targets. The same effect can be achieved by using specific ribozymes, which are oligonucleotides as well (claim 4).

Another way of inhibiting the signal pathway of molecules negatively effecting the immune system is achievable by binding a part of an antibody (Fab fragment or single chain antibody) to the above mentioned targets. A target molecule to which a part of an antibody is bound will not be able to activate its specific receptor and by this the down regulation of the immune system. In the same way, a receptor to which a part of an antibody is bound will no longer be available for its target molecule (e.g., TGF-beta, VEGF etc.). Also in this way, the down regulation of the immune system is blocked.

This illustrates that all substances mentioned in claims 1 to 6 have the common effect of blocking the signal pathways of substances negatively effecting the immune response. This common

effect allows, according to MPEP § 806.04 and MPEP § 808.01, combining these substances in one single application. Therefore, the inventions I and II, respectively II and IV, according to the proposal of the USPTO, are consistent. Inventions I and III, respectively II and IV, representing the treatment of an infectious disease and a neoplasm, are consistent as well.

That is, the immune system plays a key role in the inventions I/II and III/IV disease groups. Even if therapeutic treatment reduces bacteria, viruses, and parasites causing infectious diseases, the immune system has to finalize this treatment by eradicating the infectious agent, completely.

In the same way, in cancer therapy a lot of tumor cells are destroyed, e.g., by radiation or chemotherapy. Nevertheless, the remaining part of the tumor cells has to be eradicated by the immune system, itself.

This eradicating effect is only possible if the immune system works on a high (normal) level, which is not the case if the immune system is compromised by an immuno-suppressor, as mentioned in claim 1. At the same time, the immuno-suppressor is a very specific linking element for the treatment of infectious diseases and neoplasms.

Bacteria and virus as well as tumor cells can adversely effect the immune response by special escape mechanisms, e.g., they specifically suppress the immune system by over expressing a factor negatively regulating the immune system (e.g., TGF-beta). Therefore, enhancing the immune system by inhibiting the immuno-suppressors, and combining this effect with the effect of substances stimulating the immune system, will result to treatment of infectious diseases and neoplasms.

In conclusion, inventions I to IV are not properly restricted, but are based on a unified concept.

Applicant submits that restriction of invention V appears based on a misunderstanding of claim 9. Claim 9 defines a medicament comprising two or more of the inhibitors and/or two or more of the stimulators of claim 1. This claim uses the expression "at least one," which is used in claim 1 for both the stimulators and the inhibitors. Therefore claim 9 is not properly restricted from claim 1.

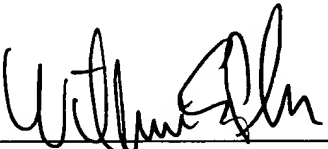
Traverse is also maintained in that no reasoning is provided for requiring election from among elements of claim 1 and claim 8.

Favorable action is requested.

Respectfully submitted,

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